42. (New) The method of claim 40, wherein said collective ligand variant population comprises nucleic acid ligands.

43. (New) The method of claim 40, wherein said collective ligand variant population comprises polypeptide ligands.

44. (New) The method of claim 40, wherein said collective ligand variant population comprises carbohydrate ligands.

45. (New) The method of claim 40, wherein said collective ligand variant population comprises lipid ligands.--

REMARKS

Claims 1-39 are pending in the application and claims 10-18 and 39 are under examination in the application. Claims 1-9 have been cancelled herein without prejudice. Applicants respectfully request that claims 19-38 remain pending in the application until indication of allowable subject matter. Claims 10, 11, 13, 14, 17 and 18 have been amended and new claims 40-45 have been added. Support for the amendments and new claims can be found throughout the specification and claims as filed. In particular, support for the amendments to claims 10, 11, 13, 14, 17 and 18 can be found, for example, at page 12, lines 25-29, and at page 9, line 32, to page 10, line 1. Support for new claims 40-45 can be found, for example, at page 8, lines 11-13. In

addition, support for claim 41 can be found at page 9, lines 26-28. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants respectfully submit that entry of the amendments after final is proper because the amendments place the claims into condition for allowance or in better form for consideration on appeal, and do not raise new issues for consideration in accordance with 37 CFR 1.116 and MPEP 714.12 and 714.13. Therefore, entry of the amendments is respectfully requested.

Applicants have set forth above the amendments to the specification and claims in clean form as required under 37 C.F.R § 1.121 (c)(i). Applicants also attach Appendix A with the marked amendments to the specification and claims indicated with brackets and underlining as required under 37 C.F.R. § 1.121 (c)(ii).

The present invention provides a method for determining optimal binding of ligands to receptors. The method consists of contacting a collective ligand variant population with receptors and detecting binding of receptors to the collective ligand variant population. The collective ligand variant population contains ligands structurally related to a parent or target ligand. The collective ligand variant population can be further divided into two or more sub-population which can be contacted with more receptors and binding detected. In addition, the steps

of dividing, contacting and detecting can be repeated one or more times. Applicants have reviewed the Office Action and respectfully traverse all grounds for rejecting the claims for the reasons that follow.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 10-18 and 39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. The Office Action acknowledges that terms such as "collective ligand variant population," "binding activity," and "optimal binding activity" are defined in the specification, but alleges that they are defined very broadly. Specifically, the Office Action alleges that the "collective ligand variant population" recited in the claims could encompass a virtually unlimited number of compounds and that the claims could encompass an infinite number of variations.

Applicants submit that the specification provides sufficient description and guidance to convey to one skilled in the art the structural and functional features of a "collective ligand variant population." For example, the specification teaches that the collective ligand variant population is comprised of ligands that are variations of a parent or target ligand. The specification at page 8, lines 26-28, defines the term "variant" when used in reference to a ligand as a molecule

that shares a similar structure and function. In addition, the specification teaches that the characteristics that define the function can be determined by a parent ligand, and that variants can possess, for example, substantially the same or similar binding function as the parent molecule (page 8, lines 29-32). The specification goes on to teach different modifications of a parent molecule that can result in variants such as, for example, mutation of an amino acid residue, addition of a chemical moiety, or binding of a regulatory molecule (page 9, lines 3-25). Thus, a collective ligand variant population is not a random mixture of ligands, but instead has structural and functional features based on a particular parent ligand.

The Office Action further alleges that the specification does not describe an example of a collective ligand variant population and that an example is required because the art is unpredictable. Applicants maintain that a working example is not required and that the art is not unpredictable. Nevertheless, Applicants submit that, based on the teachings in the specification, one skilled in the art would understand that the collective receptor variant population disclosed in Example V is also exemplary of a collective ligand variant population. The specification clearly teaches that "a molecule that is a ligand can also be a receptor and, conversely, a molecule that is a receptor can also be a ligand since ligands and receptors are defined as binding partners" (page 8, lines 16-19). In Example V, a BR96 antibody is designated as a parent receptor and used as the basis for generating a collective receptor variant population. A population of anti-idiotypic antibodies are

designated as ligands in this example. Given the teachings in the specification cited above and what was known in the art at the time of filing of the application, one skilled in the art would understand that this receptor variant population is similarly exemplary for a ligand variant population. Therefore, in addition to teaching the characteristics of a collective ligand variant population, the specification also provides an example of a population of molecules that can be a collective ligand variant population.

The Office Action also alleges that claims 15 and 16 require specific techniques for producing ligands which are not adequately described in the disclosure. In addition, the Office Action alleges that claim 17 and claim 39 require tagging which is not adequately described in the disclosure. Further, the Office Action alleges that there are no examples of these techniques.

Applicants submit that the specification provides sufficient description to teach one skilled in the art how to recombinantly express a ligand variant population in cells (claim 15) and specifically in melanophore cells (claim 16). Using the description and guidance in the specification, Applicants contend that it would have been clear to one of skill in the art how to produce ligands by recombinant expression in cells. For example, procedures for generating DNA constructs and performing transfections were well known in the art and referenced in the specification (see reference to Sambrook et al., 1989, for example, at page 39 lines 3-5). In addition, specific procedures

for deriving melanophore cells (page 37, line 15, to page 38, line 5) and transfecting DNA constructs into melanophore cells (page 39, lines 1-10) are taught in Example I of the specification. Although Example I and the above-indicated reference exemplify expression of a receptor DNA construct in melanophore cells, one skilled in the art would clearly understand that a ligand DNA construct could be expressed in melanophore cells using the same procedure. As corroboration that one skilled in the art would have known how to express constructs other than receptor constructs in melanophores, Applicants submit as Exhibit A U.S. Patent No. 5,462,856 which was cited on Form PTO 1449. On column 13, lines 45-48, the patent describes an example using electroporation of a lacZ plasmid into melanophore cells. In addition, on column 14, lines 55-58, the patent describes that exogenous G proteins can be expressed in melanophores via the type of recombinant DNA technology used to express GPCRs in melanophores.

In regard to tagging ligands, the specification teaches methods of tagging variants at page 28, line 28, to page 30, line 24. For example, the specification teaches that a large number of tags can be generated with a limited number of different peptides and antibodies specific for those peptides (page 29, lines 30-32). In addition, the specification gives an example of the use of 32 different peptides to generate 4096 different tags (page 30, lines 1-4). Furthermore, the specification teaches methods for detecting the tag, for example, using antibodies specific for the peptides in FACS analysis (page 30, lines 8-20). Moreover, the specification provides an example, Example I, where

a variant population is tagged by co-expression of a peptide tag on the parental expression vector (page 38, lines 18-33). Again, although Example I exemplifies tagging of a receptor DNA construct, one skilled in the art would clearly understand that a ligand DNA construct could be tagged using the same procedure.

Applicants respectfully submit that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Therefore, Applicants respectfully request that these grounds of rejection be withdrawn.

Claims 10-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. The Office Action alleges that the specification does not provide adequate support for the term "two or more receptors."

Applicants submit that the language of the claims, as amended, is sufficiently supported in the specification. The claims are directed to methods for determining binding of a ligand to a receptor by contacting a collective ligand variant population with a population of five or more receptors and detecting binding of a receptor to the collective ligand variant population. Support for the term "population of five or more receptors" can be found, for example, at a page 12, lines 25-29, which indicates that a population of receptors can be screened with a ligand variant population, and at page 9, line 32, to page 10, line 1, which indicates that populations can be between 5 and

10 species as well as up to hundreds or thousands of different species. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Regarding the recitation of the term "population of two or more receptors" in new claim 41, Applicants point to support for this term at page 9, lines 26-28, which indicates that the term population can refer to a group of two or more different molecules.

Claims 10-18 and 39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action alleges that the claims and nature of the invention regarding ligands and receptors are broad and that the state of the art is unpredictable. Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods.

Regarding the alleged breadth of the claims in regard to the structure of the collective ligand variant population, as described earlier, the specification teaches that a collective ligand variant population is not a random mixture of ligands, but instead has structural and functional features based on a particular parent ligand. Furthermore, the specification teaches in detail several methods for creating variants including codon-based mutagenesis (pages 20, line 18, to page 23, line 6, and Example V, page 49, line 10, to page 50, line 28). Based on the teachings in the specification regarding ligands and receptors, an methods understood by one skilled in the art, these methods

for creating variants are equally applicable to a ligand variant population or a receptor variant population.

Regarding the alleged unpredictability in the art, Applicants respectfully submit that the specification provides sufficient description and guidance to enable the invention as claimed. The Office Action acknowledges that ligand/receptor binding pairs were well-known in the art at the time of the invention, however the Office Action alleges that only limited numbers of such pairs were known. Applicants submit that a number of ligand/receptor binding pairs were known in the art at the time of filing of the application, thus contributing to predictability in the art. For example, attached herewith as Exhibit B is a review article by Power and Wells describing a number of chemokine receptors, which are G-protein coupled receptors, and their corresponding ligands (Trends in Pharm. Sci., 17:209-212 (1996), see in particular page 211, Table 1, exemplifying 10 receptor/ligand pairs). In addition, attached herewith as Exhibit C is a review article by Bazzoni and Beutler describing several TNF receptor and ligand pairs (N. Engl. J. Med. 334:1717-1725 (1996), see in particular page 1719, Table 1, exemplifying 10 receptor/ligand pairs). Furthermore, attached herewith as Exhibit D is a review article by Fantl et al. describing several receptor tyrosine kinases and corresponding ligands (Annu. Rev. Biochem. 62:453-481 (1993), see in particular page 455, Figure 1, exemplifying 9 receptors with known ligands). Thus, these publications demonstrate that a number of ligand/receptors binding pairs with diverse structures were known in the art at the time of filing of the application.

Regarding unpredictability in the use of melanophore cells and adding tags to ligands, Applicants submit that the specification teaches methods of using melanophore cells to express variants (page 24, line 11, to page 25, line 32; Example I, pages 37-40) and methods for tagging with an identifiable tag (page 28, line 18, to page 30, line 24; and Example I, page 38, lines 18-33). As described further above, Applicants submit that one skilled in the art would know how to express a ligand in melanophore cells using the teachings in the specification. Therefore, Applicants submit that undue experimentation would not be required to express a ligand or a receptor in a melanophore cell. Regarding the alleged unpredictability of adding tags to ligands, the Office Action cites an article by Janda (Proc. Natl. Acad. Sci. USA 91:10779-10785 (1994)) as describing the unpredictability of tagging methods. However, the article by Janda cites several references that have successfully used different tagging methods. These methods include diverse tagging strategies such as phage display, a "peptides on plasmids" method by Affymax, a peptide coded library method by Chiron Corporation, electrophoric tagging, and encoded combinatorial libraries. Thus, Janda supports the teachings in the specification that one skilled in the art would expect to successfully tag a ligand variant population without undue experimentation.

The Office Action again alleges that no working examples of the claimed methods are provided. As discussed above, a working example is not required; however, a working example in the specification (Example V) describing receptor variants, is exemplary for ligand variants. Furthermore,

guidance in the specification on page 31, lines 5-8, clearly states that methods and procedures for determining binding of a receptor to one or more ligands can similarly be applied to determine the binding of a ligand to one or more receptors.

Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicants respectfully request that these grounds of rejection be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 10-14, 17 and 18 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Combs et al. (J. Am. Chem. Soc. 118:287-288 (1996)). The Examiner alleges that Combs et al. discloses a method for using a library of ligands that direct non-peptide binding elements into the specificity pocket of an SH3 protein and that the library was tagged and decoded to find an optimal binding ligand.

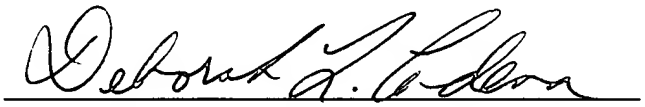
Applicants respectfully submit that the claims are novel over the Combs et al. reference. The claims, as amended, are directed to methods for determining binding of a ligand to a receptor by contacting a collective ligand variant population with a population of five or more receptors and detecting binding of a receptor to the collective ligand variant population. Combs et al. does not teach contacting a collective ligand variant population with five or more receptors. Thus, the Combs et al. reference does not teach the method of the claimed invention and,

therefore, it cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,



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